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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/149,718	09/08/98	GAMES K	ANS-101-CIP(

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EXAMINER	
CROUCH, D	
ART UNIT	**PAPER NUMBER**
1632	5

DATE MAILED: 04/27/00

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/149,718	Games et al.
Examiner	**Group Art Unit**
Deborah Crouch	1632

☐ Responsive to communication(s) filed on _____

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *three (3)* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claim

☒ Claim(s) *1-20, 22-26, and 28-56* is/are pending in the applicat

Of the above, claim(s) _____ is/are withdrawn from consideration

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-20, 22-26, and 28-56* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☒ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____ .

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). *3*

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

— SEE OFFICE ACTION ON THE FOLLOWING PAGES —

This is a CIP of 08/480,653, filed June 7, 1995, now abandoned.

There appears to be several applications to related subject matter with same assignee. Applicant is requested to indicate in the response to this office action any other applications so related.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornum,* 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); and *In re Goodman,* 29 USPQ2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.78(d).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-20,22-26 and 28-56 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7,9-16 and 18-26 of copending Application No. 09/149,856. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and '856 are obvious over each other. Claims 1-20,22-26 and 28-56 of the instant application are drawn to a method of testing compounds for an effect on Alzheimer's Disease comprising administering a test compound to a transgenic mouse or cells derived from the transgenic mouse whose genome comprises a nucleic acid construct where the construct comprises a region encoding an Aβ-containing peptide operably linked to a promote, where the mouse and the cells express the Aβ-containing peptide at very specific levels at very specific ages, and detecting or measuring the effect of the compound on an Alzheimer's Disease marker in the mouse or cells. The Aβ-containing peptide is claimed to be one of many such peptides, and the markers are expression of certain proteins and/or the formation of certain Alzheimer's Disease related morphological or behavior phenotypes, and a reduction in the amount of nucleic acid present in the mouse. The mouse of the instant assay can be made either with or without a construct comprising introns and exons of the APP genomic sequence. Claims 1-7,9-16 and 18-26 of '856 are drawn to a transgenic mouse whose genome

comprises and expresses a nucleic constructs, where the construct comprises a region encoding an Aβ-containing peptide operably linked to a promote, where the mouse and the cells express the Aβ-containing peptide at very specific levels at very specific ages. The mouse and cells of '856 comprise or do not comprise a transgene comprising introns and exons of the APP genomic sequence. The instantly claimed method is obvious over the mouse and cells claimed in '856 because the a use for the mouse is in the method of assay. Thus, at the time of the instant invention, the ordinary artisan would have found the instant invention obvious over that of claims 1-7,9-16 and 18-26 of '856 as the instant method would obviously have required the mouse claimed in '856.

This is a provisional obviousness-type double patenting rejections because the conflicting claims have not in fact been patented.

Claims 1-20,22,23,26,29-50,53 and 54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,811,633. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are drawn to a method of testing compounds for an effect on Alzheimer's Disease comprising administering a test compound to a transgenic mouse or cells derived from the transgenic mouse whose genome comprises a nucleic acid construct where the construct comprises a region encoding an Aβ-containing peptide operably linked to a promote, where the mouse and the cells express the Aβ-containing peptide at very specific levels at very specific ages, and detecting or measuring the effect of the compound on an Alzheimer's Disease marker in the mouse or cells. The Aβ-containing peptide is claimed to be one of many such peptides, and the markers are expression of certain proteins and/or the formation of certain Alzheimer's Disease related morphological or behavior phenotypes, and a reduction in the amount of nucleic acid present in the mouse. The mouse of the instant assay is claimed to be made with any number of APP transgenes including a transgene comprising introns and exons of the APP genomic sequence. The mouse of '633 is claimed to comprise a specific transgene construct which comprises intron and exon sequences of the APP genomic sequence substituted into an APP770 cDNA or an APP770 comprising naturally occurring mutations, and wherein expression of the construct results in the differential

expression of splice variants APP695, APP751 and APP770 mRNA and protein in detectable levels in the brains of the mice. As the mouse used in the instantly claimed assay is stated to encompass or have a transgene that comprises exon and introns sequences of the APP genomic sequence operably linked to any promoter, and this language is the language of the mice of '633, the method of assay is obvious over the mouse of '633. A product and its properties can not be separated. Therefore the mouse of '633 would inherently develop the characteristics and features of the mouse of the instantly claimed assay. The mouse of '633 is defined as being useful for assaying compounds to treat symptoms of Alzheimer's Disease. Therefore, at the time of the instant invention, the assay of instant claims 1-20,22,23,26,29-50,53 and 54 would have been obvious to the ordinary artisan given claims 1-6 of '633.

Claims 1-20,22,23,36,29-50,53 and 54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,720,936. Although the conflicting claims are not identical, they are not patentably distinct from each other. The instant claims are drawn to a method of testing compounds for an effect on Alzheimer's Disease comprising administering a test compound to a transgenic mouse or cells derived from the transgenic mouse whose genome comprises a nucleic acid construct where the construct comprises a region encoding an Aβ-containing peptide operably linked to a promote, where the mouse and the cells express the Aβ-containing peptide at very specific levels at very specific ages, and detecting or measuring the effect of the compound on an Alzheimer's Disease marker in the mouse or cells. The Aβ-containing peptide is claimed to be one of many such peptides, and the markers are expression of certain proteins and/or the formation of certain Alzheimer's Disease related morphological or behavior phenotypes, and a reduction in the amount of nucleic acid present in the mouse. The mouse of the instant assay is claimed to be made with any number of APP transgenes including a transgene comprising introns and exons of the APP genomic sequence. The assay claimed in '936 is claimed employ a mouse comprising a specific transgene construct which comprises intron and exon sequences of the APP genomic sequence substituted into an APP770 cDNA or an APP770 comprising naturally occurring mutations, and wherein expression of the construct results in the differential expression of splice variants APP695, APP751 and APP770 mRNA and protein in

detectable levels in the brains of the mice. As the mouse used in the instantly claimed assay is stated to encompass or have a transgene that comprises exon and introns sequences of the APP genomic sequence operably linked to any promoter, and this language is the language of the mice of the assay in '936, the instant method of assay is obvious over the assay of '936. A product and its properties can not be separated. Therefore the mouse of the assay in '936 would inherently develop the characteristics and features of the mouse of the instantly claimed assay. Therefore, at the time of the instant invention, the assay of instant claims 1-20,22,23,26,29-50,53 and 54 would have been obvious to the ordinary artisan given claims 1-6 of '936.

Claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 5,612,486. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant application and '486 are obvious over each other. Claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56 of the instant application are drawn to a method of testing compounds for an effect on Alzheimer's Disease comprising administering a test compound to a transgenic mouse or cells isolated from the transgenic mouse containing a nucleic acid construct encoding a human APP with amino acids substitutions at position 670/671 operably linked to a mammalian promoter expressing APP at certain levels and detecting or measuring the effect of the compound on an APP or Aβ marker, and where the marker is specifically claimed as any number of proteins. The claims of '486 are to a non-human transgenic mammals which expresses a nucleic acid construct encoding a Swedish mutant APP695 at amino acid positions 595 and 596. Note that the claimed mutations of 670 and 671 of APP770 are the same mutations but given in reference to the APP770 splice variant of APP695. Both the claims of the instant application and the claims of '486 state that the mouse of the claims has an identical transgene. As product and its properties can not be separated, the mouse employed in the instant assay and the mouse of '486 would inherently have the same characteristics. Thus, the ordinary artisan at the time of the instant invention would have found the method of assay of claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56 obvious over

the mouse of claims 1-4 in '486. The mouse of '486 is defined by the specification as being an assay for compounds that can be used in the treatment of Alzheimer's Disease.

Claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 6 and 10-12 of U.S. Patent No. 5,604,102. Although the conflicting claims are not identical, they are not patentably distinct from each other. Claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56 of the instant application are drawn to a method of testing compounds for an effect on Alzheimer's Disease comprising administering a test compound to a transgenic mouse or cells isolated from the transgenic mouse containing a nucleic acid construct encoding a human APP with amino acids substitutions at position 670/671 operably linked to a mammalian promoter expressing APP at certain levels and detecting or measuring the effect of the compound on an APP or Aβ marker, and where the marker is specifically claimed as any number of proteins. The claims of '102 are to a method of assay employing non-human transgenic mammals which expresses a nucleic acid construct encoding a Swedish mutant APP695 at amino acid positions 595 and 596. Note that the claimed mutations of 670 and 671 of APP770 are the same mutations but given in reference to the APP770 splice variant of APP695. Both the claims of the instant application and the claims of '102 state that the mouse of the claims has an identical transgene. As product and its properties can not be separated, the mouse employed in the instant assay and the mouse of '102 would inherently have the same characteristics. Thus, the ordinary artisan at the time of the instant invention would have found the method of assay of claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56 obvious over the method of assay in claims 6 and 10-12 in '102. The mouse of '102 is defined by the specification as being an assay for compounds that can be used in the treatment of Alzheimer's Disease.

Claims 1-20,22,23,26,29-50,53 and 54 directed to an invention not patentably distinct from claims 1-6 of commonly assigned 5,811,633. Specifically, instant claims 1-20,22,23,26,29-50,53 and 54 are drawn to a method of assay using a mouse of the same scope as the mouse of claims 1-6 pf '633. Since a product and its properties can not be separated, the mice of the instant assay would inherently encompass

the mice of '633. Further the mice of '633 are defined to be an assay for Alzheimer's Diseases therapeutics. Thus there is no patentable distinct between the instant claims and those of '633.

Claims 1-20,22,23,26,29-50,53 and 54 are directed to an invention not patentably distinct from claims 1-6 of commonly assigned U.S. Patent 5,720,936. Specifically, instant claims 1-20,22,23,26,29-50,53 and 54 and claims 1-6 pf '936 are both drawn to methods of assay using mice that are of the same scope. The mice of the instant assay comprise the same transgene construct as the transgene construct of '936. Since a product and its properties can not be separated, the instant assay would inherently encompass the assay of '936. Thus there is no patentable distinct between the instant claims and those of '936

Commonly assigned U.S. Patent 5,811,633 and U.S. Patent 5,720,936, discussed above, would form the basis for a rejection of the noted claims under 35 U.S.C. 103(a) if the commonly assigned case qualifies as prior art under 35 U.S.C. 102(f) or (g) and the conflicting inventions were not commonly owned at the time the invention in this application was made. In order for the examiner to resolve this issue, the assignee is required under 37 CFR 1.78(c) and 35 U.S.C. 132 to either show that the conflicting inventions were commonly owned at the time the invention in this application was made or to name the prior inventor of the conflicting subject matter. Failure to comply with this requirement will result in a holding of abandonment of the application.

A showing that the inventions were commonly owned at the time the invention in this application was made will preclude a rejection under 35 U.S.C. 103(a) based upon the commonly assigned case as a reference under 35 U.S.C. 102(f) or (g).

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1,2,5-20,24-26,28-30,33-48,51053 and 56 are rejected under 35 U.S.C. 102(a) as being clearly anticipated by WO 95/11968. '968 teaches a method for identifying drugs effective in the treatment of Alzheimer's Disease wherein the assay comprising administering drugs of interest to transgenic non-human mammals that express the Swedish mutation APP operatively linked to the rat NSE promoter (page 39-40, bridg. parag.; page 41, lines 16-22 and page 42, lines 17-24). As the construct disclosed in '986 is also claimed by applicant, the expression levels, characteristics and features claimed for the mouse of the instant assay are an inherent feature of the mouse of the assay in '968. The instant specification defines the promoter as being the rat neuron specific enolase promoter (specification, page 11). Thus, '968 clearly anticipates the instant invention.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-20,22,23,26,29-50,53 and 54 1-11 and 14-17 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by WO 93/14200. '200 teaches a method of screening for compounds effective in the treatment of Alzheimer's Disease wherein the treatment assay comprises transgenic mice or transformed cells that express a transgene encoding APP770, APP751, APP695, APP770 with FAD mutations at amino acid 717 operably linked to the PDGFβ promoter (page 14, parag. 1, page 15, parag. 1, page 16, parag. 1, pages 18, parag. 1, lines 4-5 and pages 28-30). The construct disclosed in '200 is the same as that claimed by applicant, and as such the expression levels, characteristics and features of the mouse of the assay claimed by applicant are an inherent feature of the mouse testing model disclosed in '200. Thus '200 clearly anticipates the claimed invention.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-20,22,23,26,28-50 and 53-56 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent No. 5,720,936 issued February 24, 1998.

'936 teaches the an assay system comprising transgenic mice whose genome comprises and expresses a variety of APP transgene constructs: cDNA encoding APP770, APP751, APP695 and FAD mutants of these cDNA's and a cDNA genomic construct, a specific version of which is claimed (col. 8, 13-22, lines 46 to col. 9, line 23; and claims 1-6). The construct is disclosed and claimed to be operatively linked to a promoter, and such as the PDGF promoter (col. 9, lines 60-64 and claims 1,3 and 4). As the specification of '936 teaches mice having the same construct as the mice of the instantly claimed methods of screening, those mice of '936 would inherently develop the features and characteristics instantly claimed for the mouse of the screening assay. A product and its features can not be separated. Thus '936 clearly anticipates the claimed invention.

Claims 1,2,5-20,24-26,28,29,33-45,51-53 and 56 are rejected under 35 U.S.C. 102(e) as being clearly anticipated by U.S. Patent No. 5,604,102 issued February 18, 1997.

'102 teaches a method of assay employing a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (col. 15, lines 26-31 and col. 20, lines 16-20, and claims 1-16). These mutations are identical to K670M, N671L. The variation in numbering is due to '102 referring to the APP695 numbering and the instant claims to the APP770 numbering. APP695 K670M, N671L is specifically claimed. The specification clearly defines the NSE promoter as one promoter to be used in the instant claims. As the mice of the assay in '102 are claimed to encompass the same transgene as that of the assay of '102, those mice would inherently develop the characteristics and features of the mice of the instantly claimed assay. Thus, '102 clearly anticipates the claimed invention.

(f) he did not himself invent the subject matter sought to be patented.

Claims 1-20,22,23,26,28-50 and 53-56 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

U.S. Patent No. 5,720,936 issued February 24, 1998 teaches the an assay system comprising transgenic mice whose gemone comprises and expresses a variety of APP transgene constructs: cDNA

encoding APP770, APP751, APP695 and FAD mutants of these cDNA's and a cDNA genomic construct, a specific version of which is claimed (col. 8, 13-22, lines 46 to col. 9, line 23; and claims 1-6). The construct is disclosed and claimed to be operatively linked to a promoter, and such as the PDGF promoter (col. 9, lines 60-64 and claims 1,3 and 4). '936 is presently commonly assigned to Athena Neurosciences. The record indicates that at the time of invention '936 was assigned to TSI Corporation in paper no. 3 filed August 31, 1992. There is no evidence of record that at the time of the invention disclosed in '936, that the invention was assigned to Athena Neurosciences. Thus, applicant must provide information that the instant invention and the invention disclosed in '936 were commonly owned at the time of the invention disclosed in '936. Thus there is evidence that the instant applicant did not invent the instant invention, that another had made applicant's invention prior to applicant who had not suppressed or concealed it and that the instant invention and that of '936 were not commonly owned at the time that '936 was invented. Applicant is referred to MPEP 706.02(l).

Claims 1,2,5-20,24-26,29,33-45,51-53 and 56 are rejected under 35 U.S.C. 102(f) because the applicant did not invent the claimed subject matter.

U.S. Patent No. 5,604,102 issued February 18, 1997 teaches a method of assay employing a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (col. 15, lines 26-31 and col. 20, lines 16-20, and claims 1-16). These mutations are identical to K670M, N671L. The variation in numbering is due to '102 referring to the APP695 numbering and the instant claims to the APP770 numbering. APP695 K670M, N671L is specifically claimed. The specification clearly defines the NSE promoter as one promoter to be used in the instant claims. There is no evidence of record that Athena Neurosciences was the assignee of the invention of '102 at the time that the application for '102 was filed. Application serial no. 08/143,697 provides for no assignment at the time of filing, October 27, 1993. Thus there is evidence that the instant applicant did not invent the instant invention, that another had made applicant's invention prior to applicant who had not suppressed or concealed it and that the instant invention and that of '102 were not commonly owned at the time that '102 was invented. Applicant is referred to MPEP 706.02(l).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1,2,5-20,26,29,30,33-48,53 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent 5,387,742 issued February 7, 1995.

'742 teaches the production of transgenic mice expressing DNA sequences encoding APP770,APP751,APP695,A42,A99,A4i from the NSE or metallothionein promoters (claims and col. 14, line 65 to col. 15, line 11). These mice produce brain morphologies such as neuritic process in the hippocampal and cortical neurons of their brains as a result of the expression of the transgenes (col. 32, lines 34-56). '742 discloses, and offers motivation, that the transgenic mice can be used as screening assays to identify compounds useful in the treatment of Alzheimer's Disease (col. 34, line 38 to col. 35, line 1). Thus, at the time of the instant invention, it would have been obvious to employ the mouse of '742 in an assay system to determine compounds useful for the treatment of Alzheimer's Disease.

Claims 1,3,4,22-25 and 49-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over either U.S. Patent 5,387,742 issued February 7, 1995 in view of Sasahara et al (1991) Cell 64, 217-227 in view of any of Mullen et al (1992) Nature Genetics 1, 345-347, Chartier-Harlin et al (1991) Nature 353, 844-846 and Hendriks et al (1992) Nature Genetics 1, 218-221.

'742 teaches the production of transgenic mice expressing DNA sequences encoding APP770,APP751,APP695,A42,A99,A4i from the NSE or metallothionein promoters (claims and col. 14, line 65 to col. 15, line 11). These mice produce brain morphologies such as neuritic process in the hippocampal and cortical neurons of their brains as a result of the expression of the transgenes (col. 32, lines 34-56). '742 discloses that the transgenic mice can be used as screening assays to identify compounds useful in the treatment of Alzheimer's Disease (col. 34, line 38 to col. 35, line 1). Sasahara teaches that the PDGFβ promoter in transgenic mice preferentially expresses a reporter gene in the neural cell bodies in the

cortex, hippocampus and cerebellum (page 221, col. 2, parag. 1, lines 7-14). Mullen teaches a DNA sequence encoding APP 770 with amino acid substitutions at positions 670 and 671 (page 346, col. 2, parag. 2). This DNA sequence is associated with familial Alzheimer's Disease (page 346, col. 2, parag. 1 and parag. 2, lines 1-5). Chartier-Harlin teaches a DNA sequence encoding APP770 with an amino acid substitution at position V717G, at V717I and at V717F (page 844, col. 2, parag. 2, lines 6 and 10-12; and page 845, col. 1, parag. 1, lines 6 and 10-12 and col. 2, parag. 2)). Chartier-Harlin also teaches that this DNA sequence is associated with a familial form of Alzheimer's Disease (page 844, abstract). Hendriks teaches a DNA sequence encoding APP770 with an amino acid substitution at position A692G (page 219, col. 2, parag. 1, lines 1-8). Hendriks also teaches that this DNA sequence is associated with a familial form of Alzheimer's Disease and that individuals with this FAD form amyloid plaques (page 219, col. 2, parag. 3, lines 6 and 10-12 and page 220, col. 1, parag. 2, line 1 to col. 2, lines 2). Each of Mullen, Chartier-Harlin and Hendriks teaches the wild type APP770 sequence. These cited references provided the artisan with sufficient guidance and motivation in producing transgenic mice expressing an Alzheimer's Disease related APP so that the mice could be an assay system to identify compounds effective in the treatment of Alzheimer's Disease. The determination of other Alzheimer's Disease related markers such as tau, GFAP, and behavioral and cognitive functions would have been obvious to the ordinary artisan at the time of the instant invention. As '742 teaches the formation of Alzheimer's related pathologies in transgenic mice expressing APP770 in hippocampal and cortical neuronal cells in view of Sasahara teaching that the PDGFβ promoter regulates expression of a heterologous DNA sequence in hippocampal and cortical neuronal cells, there would have been a reasonable expectation of success in producing transgenic mice which merely express one of the Alzheimer's Disease related mutant APP sequences taught by Mullen, Charier-Harlin and Hendriks. Thus given the cited prior art, it would have been obvious to the ordinary artisan at the time of the instant invention to produce transgenic mice for a method of assay. Mullen provides motivation in stating that DNA sequence disclosed therein increases the likelihood of producing transgenic animals with Alzheimer's pathology (page 347, col. 2, lines 6-9). The artisan would have at the time of the instant invention realized the motivation of Mullen would apply to the APP DNA sequences of Chartier-Harlin and

Hendriks in the production of Alzheimer's Disease models. Absent results to the contrary, the expression levels obtained in these transgenic mice would be expected to achieve the same expression levels as they would contain the same components as those claimed by applicant. The claims as written provide no unexpected results over the cited prior art or non-obvious embodiments of the assay system. Further, the isolation of cells from tissues was well known in the art at the time of filing and would have been within the scope of cells of the ordinary artisan to establish cultures from transgenic non-human mammal tissue for the cells to become a drug testing assay.

Claims 1-20,22,23,26,29-50,53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over Games et al (1995) Nature 373, 523-527. Games et al teach, and thereby offers motivation, that the transgenic mice disclosed therein can be used to determine the effectiveness of compounds that lower Aβ production in vitro in an in vivo assay (page 527, col. 1, parag. 1, lines 8-13). The transgenic mice are taught to express a transgene encoding APP770 V717F operatively linked to the PDGFβ promoter and to develop brain morphologies associated with Alzheimer's Disease: dense plaques, GFAP, neuritic processes, synaptophysin and MAP-2 (page 524, col. 2, parag. 1, lines 10-12 and page 526, col. 1, lines 19-21; col. 1-2, bridg, sent. and col. 2, lines 11-14). As the mouse of Games et al expresses the same transgene construct as claimed by applicant, the particular characteristics claimed for the mouse of the instant assay are obvious features for the mouse of Games et al. Therefore, it would have been obvious to the ordinary artisan to employ the mouse of Games et al as an assay for therapeutics in the treatment in Alzheimer's Disease.

Claims 1-20,22,23,26,29-50,53 and 54 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,811,633.

'633 teaches a transgenic mice whose gemone comprises and expresses a variety of APP transgene constructs: cDNA encoding APP770, APP751, APP695 and FAD mutants of these cDNA's and a cDNA genomic construct, a specific version of which is claimed (col. 7, line 65 to col. 8, line 8, line 32 to col. 9, line 8 and claims 1 and 3-6). The construct is disclosed and claimed to be operatively linked to a promoter, and such as the PDGF promoter (col. 9, lines 43-48 and claims 1 and 6). The mice are taught to

be an assay model for determining compounds for the treatment of Alzheimer's Disease (col. 15, lines 31-40). As the specification of '633 teaches mice having the same construct as the mice of the instantly claimed methods of screening, those mice of '633 would inherently develop the features and characteristics instantly claimed for the mouse of the screening assay. A product and its features can not be separated. Therefore at the time of the instant invention, it would have been obvious to the ordinary artisan to employ the mice of '633 as an assay system for identifying compounds for an effect on Alzheimer's Disease.

Claims 1,2,5-20,24-26,28-30,33-48,51-53 and 56 are rejected under 35 U.S.C. 103(a) as being unpatentable over U.S. Patent No. 5,612,486.

'486 teaches a transgenic mouse whose genome comprises a transgene comprising APP695 K595M, N596L, the Swedish mutation operably linked to the NSE promoter (col. 13, line 56-66; col. 24, lines 45-53 and col. 20, lines 16-20, and claims 1-16). These mutations are identical to K670M, N671L. The variation in numbering is due to '486 referring to the APP695 numbering and the instant claims to the APP770 numbering. APP695 K670M, N671L is specifically claimed. The mice of '486 are taught to be useful in screening assays to determine pharmaceuticals for treating Alzheimer's Disease (col. 23, lines 44-50).The specification clearly defines the NSE promoter as one promoter to be used in the instant claims. As the mice of the assay in '486 are claimed to encompass the same transgene as that of the assay of '486, those mice would obviously develop the characteristics and features of the mice of the instantly claimed assay. Therefore, at the time of the instant invention, it would have been obvious to the ordinary artisan to employ the mice of '486 as an assay system for identifying compounds for an effect on Alzheimer's Disease.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-20,22-26 and 28-56 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for methods for testing or screening compounds for an effect on an Alzheimer's disease marker wherein a compound of interest is administered to transgenic mice whose somatic and germ cells contain a nucleic acid construct comprising a PDGFβ promoter operatively linked to a cDNA-genomic DNA hybrid sequence, wherein said hybrid sequence contains a cDNA sequence encoding APP770 with a mutation of valine for phenylalanine at position 717, wherein a genomic APP DNA sequence consisting of exon 6 and an amount of the adjacent downstream intron sufficient for splicing, the KI and OX-2 coding region and an amount of each of their upstream and downstream introns sufficient for splicing, and exon 9 and an amount of the adjacent upstream intron sufficient for splicing is substituted into the corresponding region of the cDNA sequence encoding APP770 with a mutation of valine for phenylalanine at position 717, wherein expression of the transgene results in the claimed phenotype at 2-4 months of age, and where the Alzheimer disease marker is an increase or decrease in a protein selected from the group consisting of synaptophysin, GFAP, phosphorylated tau, phosphorylated neurofilaments, MAP-2, Aβtot, Aβ1-42, Aβ1-40, FLAPP + APPα and APPβ; where the Alzheimer's disease marker is a behavior selected from the group consisting of working or reference behavior, locomotor activity, emotional reactivity and object recognition; and where the Alzheimer's disease marker is a histopathology selected from the group consisting of compact plaques, neuritic dystrophy, gliosis, Aβ deposits, decreased synaptic density and neutrophil abnormalities, does not reasonably provide enablement for the nucleic acid constructs specifically claimed and the breadth of mammals. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

At the time of filing, the production of transgenic mice which expressed in their brains a DNA sequence encoding an APP related protein was regarded as unpredictable in the resulting phenotypes of the mice varied greatly, or had no phenotype over non-transgenic age-controlled mice. Lannfelt stated that in transgenic mice expressing such a DNA sequence may not form Alzheimer's related pathologies because sufficient expression of the APP transgene may be difficult to achieve, and any expression

achieved may show an inappropriate tissue distribution (Lannfelt et al (1993) Behav. Brain Res. 57. page 210, col. 1, parag. 5; and col. 2, parag. 4, lines 8-16). Thus it appears that at the time of filing that deficiencies in the specification in providing guidance in the production of transgenic mice expressing APP sufficient to develop the claimed Alzheimer's related phenotypes could not have been overcome by a review of the relevant art. Thus the development of Alzheimer's Disease related brain pathologies in mice expressing an APP transgene is not enabled by the art or the specification, or by any post filing evidence. Furthermore, it is important to note that the mere formation of β -amyloid deposits in the brains of transgenic animals are insufficient to correlate to Alzheimer's Disease. Aged humans and monkeys are known to develop β -amyloid deposits in their brains without forming Alzheimer's Disease (Selkoe (1991) Nature 354, page 432, col. 1, parag. 3, lines 1-9 and page 433, col. 2 to col. 3). Given these teachings in the art at the time of filing, the artisan could not have depended on the art to supplement the guidance in the specification in the production of a testing assay where the assay was transgenic mice expressing various DNA sequences associated with Alzheimer's Disease and the mice had a particular 2-4 months of age phenotype. Further more the only Alzheimer's Disease markers taught by the specification to develop in the PDGF-APP mice at 2-4 months of age are is an increase or decrease in a protein selected from the group consisting of synaptophysin, GFAP, phosphorylated tau, phosphorylated neurofilaments, MAP-2, Aβtot, Aβ1-42, Aβ1-40, FLAPP + APPα and APPβ; a behavior selected from the group consisting of working or reference behavior, locomotor activity, emotional reactivity and object recognition; and a histopathology selected from the group consisting of compact plaques, neuritic dystrophy, gliosis, Aβ deposits, decreased synaptic density and neutrophil abnormalities. In particular, the HLA's specifically claimed are human antigens and would not be found in the claimed mice. Each of the additional markers are thought to be associated with Alzheimer's Disease, but there is no definitive evidence in the art or of record that indicates such, or indicates that an affect in one of these markers by administering a compound would correlate to a therapeutic for Alzheimer's Disease. Most importantly, these additionally claimed markers are taught to develop in the claimed mice, and in view of the teachings above of Lannfelt et al, it is unpredictable that phenotypes not specifically shown would develop in the PDGF-APP mice. Also it was

known in the art at the time of filing that APP695 does not produce transgenic mice that display an Alzheimer's related phenotype (Higgins et al (1993) Annals of the New York Acad. Sci. 695, pages 226-227 bridg. sent.). Articles published at the time of filing which reviewed the state of the art of Alzheimer's Disease/β-amyloid transgenic disclosed that the particular phenotype that developed in the various mice was not predictable. Sometimes only amyloid deposits were found, sometimes the deposits were associated with other AD-related brain pathologies such as neutrophil staining and behavior abnormalities (Greenberg et al and Higgins et al). Important for the instant claims is that transgenic mice comprising a transgene having the rat neuron-specific enolase promoter when linked to APP695, APP695-FAD, APP751 or APP751-751 were not shown to produce even amyloid deposits in their brains (Greenberg et al, page 159, parag. 2, lines 17-19). The instant specification discloses the rat neuron-specific enolase promoter as one to use in the claimed invention, and specifically claims APP695, APP695-FAD, APP751 and APP751-FAD as DNA sequences to be expressed. Based on the teachings of Greenberg et al, these are not enabled due to prior failures to produce mice with amyloid deposits, much less anything less, in their brains by 24 months of age. In transgenic mice expressing full length APP695, APP695-FAD, APP751 or APP751-751 from the synapsin I promoter produced amyloid in it brains, but no AD pathologies (Greenberg et al, page 160, col. 2, parag. 3, line 1-3). To cloud the issue, Greenberg reports another mouse which had as its transgene APP-751 operably linked to a rat neuron-specific enolase promoter. This mouse showed an increase in APP in its brain, neutrophil staining and certain behavior differences from non-transgenic control mice . However, the construct contained an intron sequence between the promoter and the APP751 cDNA, as well as 3' regulatory sequences. Thus, it appears that the production of a transgenic mouse with any type of AD related histopathology is dependent on the DNA construct used. Higgins et al state that the Games et al mouse, which has as a transgene a genomic DNA/cDNA hybrid sequence, demonstrates a robust phenotype and demonstrates multiple features that can be related to Alzheimer's disease such as gliosis and dystrophic neurites, and a reduction in synaptophysin and MAP-2 immunoreactivity (Higgins et al, page 122, col. 1, lines 10-21). Then, Greenberg et al states that the Games mouse is the best model of AD to date (1996) (Greenberg et al, page 161, col. 2, parag. 3, line 1).

Greenberg et al goes on to state that the Games mouse is the first to use the PDGF promoter and a construct where splicing of the transcribe RNA was possible, and that these two feature may be responsible for the high expression of APP seen (Greenberg et al, page 161, col. 1, parag. 3, lines 7-14). The Games mouse is the one specifically exemplified in the instant specification, and the one too which a scope limitation has been given. The art as summarized in Greenberg et al and Higgins et al provide further evidence that it is unpredictable to obtain any expression of APP-related proteins and peptides in transgenic mice, and that which is obtained in due to the promoter and nucleic acid used. As applicant has only taught the production of transgenic mice with the claimed APP protein and mRNA production levels and claimed Alzheimer's Disease markers by using the PDGF promoter-genomic DNA/cDNA hybrid construct as the transgene, guidance is only given for this particular construct given the above teachings and discussion. As for cells from the transgenic mice as being a testing assay, the unpredictabilities in the mice are also present in cells isolated from the mice. The specification does not teach or demonstrate that the cells from the mice would produce any hallmark feature related to Alzheimer's Disease. Furthermore, the phenotype of the claims only relates to the claimed mice, so it is not possible to determine exactly what applicant is stating that the cells represent in terms of Alzheimer's Disease. In particular, any cell from the mouse would not be representative as AD is a neurodegenerative disease. Without further guidance from the specification the skilled artisan would have needed to engage in an undue amount of experimentation without a predictable degree of success to make the claimed invention.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deborah Crouch, Ph.D. whose telephone number is (703) 308-1126.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

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